



Original article

Risk stratification of cardiovascular events in patients at all stages of chronic kidney disease using myocardial perfusion SPECT

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ABSTRACT

Background: Cardiovascular disease is the leading cause of death among patients with chronic kidney disease (CKD). Therefore, stratification of the prognostic risk of cardiovascular events is useful for their clinical management. We evaluated the ability of electrocardiogram (ECG)-gated myocardial perfusion single photon emission computed tomography (SPECT) to predict cardiac events among Japanese patients at all stages of CKD including those on hemodialysis.

Methods: Patients with CKD undergoing ECG-gated myocardial perfusion SPECT to investigate suspected ischemic heart disease were followed up to monitor retrospectively major cardiac events including cardiac death, non-fatal myocardial infarction, and unstable angina pectoris. Summed stress score, summed rest score, and summed difference score were estimated with a 20 segment 5-point scoring model. The severity of CKD was divided into five levels based on estimated glomerular filtration rate (eGFR) revised for the Japanese population.

Results: The follow-up period was 25.8 ± 11.0 months. Sixty-two major cardiac events (cardiac death, $n = 30$; non-fatal myocardial infarction, $n = 13$; unstable angina pectoris, $n = 19$) developed in 2243 patients during the first year of follow-up. The findings of multivariate Cox proportional hazards regression analysis indicated that diabetes, eGFR, the summed difference score, and summed stress score were significant independent predictors of cardiac events. The major cardiac event rate at one year increased in proportion to the progression of CKD stage. The major cardiac event-free survival rate decreased steeply over time in patients with CKD stage 5 compared with those who had CKD stages 4 or less.

Conclusion: Myocardial perfusion SPECT can contribute to the prediction of cardiac events and survival in patients at all stages of CKD including those on hemodialysis.

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Introduction

Cardiovascular disease significantly affects the prognosis of patients with chronic kidney disease (CKD). Many patients with CKD die of cardiovascular events before starting hemodialysis therapy [1]. Recent findings have demonstrated that the incidence of all death and cardiovascular events increase inversely with estimated glomerular filtration rate (eGFR). Go et al. [2] examined the multivariable association between the eGFR and the risk of death, cardiovascular events, and hospitalization among

1,120,295 adults registered in a large integrated healthcare system. At least one outpatient determination of serum creatinine levels was recorded for each registrant in a health-plan laboratory database, and they had not undergone dialysis or kidney transplantation before entry. The results of the data analyses showed that the risk of death and the hazard ratio for cardiovascular events increased inversely with eGFR. The adjusted risk of hospitalization also increased with a reduction in eGFR. Hakeem et al. [3] reported that the incidence of cardiac death, all-cause mortality, and non-fatal myocardial infarction (MI) was higher in patients with CKD ($\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$) than without ($\text{eGFR} > 60 \text{ mL/min/1.73 m}^2$) who had known or suspected cardiovascular disease. They used stress myocardial perfusion single photon emission computed tomography (SPECT) to predict adverse cardiovascular events in these patients, and emphasized the prognostic value of myocardial perfusion SPECT among patients with

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CKD. In addition, because CKD patients have a risk of contrast-induced nephropathy, myocardial perfusion SPECT is considered useful for screening coronary artery disease among such populations.

Recently, some large-scale prognostic studies using myocardial perfusion SPECT were conducted in Japan, and the study reports and the sub-analysis reports have been published one after another [4–9]. Nishimura et al. have been conducting the multicenter prospective Japanese Assessment of Cardiac Events and Survival Study (J-ACCESS), since 2001 to evaluate the prognostic value of stress myocardial perfusion SPECT in patients with suspected or confirmed ischemic heart diseases. An interim report of the J-ACCESS [4] described the prognostic data obtained from a three-year follow-up of 4031 patients. Matsumoto et al. [5] conducted a single-center prospective study to demonstrate the prognostic value of myocardial perfusion SPECT in 1846 Japanese patients with known or suspected coronary artery disease. Ohtaki et al. [6] also conducted a single-center study in 4650 consecutive patients to report a risk of severe coronary artery disease in patients indicating ischemic ST-segment changes with SPECT. Although these studies were typical Japanese large-scale prognostic studies with myocardial perfusion SPECT, they did not examine the prognostic value of myocardial perfusion SPECT in patients with CKD. Hatta et al. [7] extracted data regarding 820 patients with CKD from the J-ACCESS database to determine the prognostic value of the myocardial perfusion SPECT for cardiac events and survival. They found that the summed stress score derived from the SPECT image is a reliable predictor of cardiac events among patients with CKD. The J-ACCESS database, however, does not include information about patients with advanced renal dysfunction such as those on hemodialysis.

Therefore, we investigated whether or not ECG-gated myocardial perfusion SPECT could predict cardiac events among Japanese patients at all stages of CKD including those on hemodialysis in a large-scale follow-up study comparable to J-ACCESS.

Materials and methods

The institutional review board of Nihon University Itabashi Hospital approved this study, which proceeded in accordance with the ethical standards established in the 1964 Declaration of Helsinki. All study participants provided written informed consent prior to inclusion in this study.

Patient population

We retrospectively investigated data obtained from 2967 consecutive patients with CKD who underwent rest ^{201}Tl and stress $^{99\text{m}}\text{Tc}$ -tetrofosmin myocardial perfusion SPECT [5,10,11] to confirm or rule out suspected ischemic heart diseases at Nihon University Itabashi Hospital between October 2004 and March 2008. We excluded patients aged ≤ 20 years, those who developed acute MI or unstable angina pectoris (UAP) within three months prior to the SPECT, those with hypertrophic or dilated cardiomyopathy, serious valvular heart disease, heart failure with class III or higher New York Heart Association (NYHA) functional classification, and those without creatinine data. Follow-up examinations were based on medical records for patients who periodically attended the hospital and responses to a posted questionnaire for patients who did not. The follow-up was complete for 2611 (88%) of patients. Of these, 368 patients were excluded from prognostic analyses because they had undergone revascularization within 90 days of the SPECT examination. Data from the remaining 2243 patients were finally analyzed.

Evaluation of eGFR

The GFR was calculated from serum creatinine levels at the time of SPECT for each patient in the final prognostic analysis population using the Modification of Diet in Renal Disease Equation for Japanese Patients proposed by the Japanese Society of Nephrology [12] as follows:

$$\text{eGFR} = A \times 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287},$$

where A is 1 for men and 0.739 for women and eGFR is expressed as mL/min/1.73 m².

ECG-gated dual-isotope myocardial perfusion SPECT

The procedure of rest ^{201}Tl and stress $^{99\text{m}}\text{Tc}$ -tetrofosmin ECG-gated myocardial perfusion SPECT was performed as a protocol previously reported [5,10,11]. All patients received an intravenous (i.v.) injection of ^{201}Tl (111 MBq) and sixteen-frame gated SPECT image was initiated 10 min after injection during rest. Then an i.v. injection of $^{99\text{m}}\text{Tc}$ -tetrofosmin (740 MBq) was performed under stress induced by ergometer exercise in 31.5% of the patients or by adenosine triphosphate in 68.5%. Sixteen-frame gated SPECT image was initiated 30 min after exercise or 30–60 min after adenosine stress. No attenuation or scatter correction was used. Twelve-lead ECG was monitored continuously during stress tests. Heart rate and blood pressure were recorded at baseline and every minute for at least 3 min after stress.

SPECT image interpretation

The SPECT images were divided into 20 segments on three short-axis (distal, mid, basal) and one vertical long-axis (mid) slices, and the tracer uptake of each segment was visually scored using a 5-point scale (normal, slight, moderate, and severe reduction of uptake, 0, 1, 2 and 3, respectively; absent uptake, 4). The sum total of the scores of 20 segments in the stress and rest images provided the summed stress score (SSS) and the summed rest score (SRS), respectively. The summed difference score (SDS) was calculated as the difference between the SSS and SRS. The severity of myocardial perfusion defects was classified as normal (SSS < 4), mildly (SSS 4–8), moderately (SSS 9–13), and severely (SSS ≥ 14) abnormal. Cohen's kappa (κ), which was calculated to determine the interobserver variability for the perfusion score, was 0.92, indicating very good reproducibility.

Sixteen-frame quantitative gated SPECT data were analyzed using QGSTM software (Cedars-Sinai Medical Center, Los Angeles, CA, USA) to calculate left ventricular ejection fraction (LVEF, %), end-diastolic volume (LVEDV, mL) and end-systolic volume (LVESV, mL) as described by Germano et al. [13].

Patient follow-up

All patients were retrospectively followed up for at least one year (25.8 ± 11.0 months) after the initial stress myocardial perfusion gated SPECT. The study endpoints comprised major cardiac events within one year including cardiac death, non-fatal MI, and UAP identified from medical records or from responses to a posted questionnaire. When a patient had several cardiac events, only the first event was taken as the follow-up endpoint.

CKD staging

We defined CKD as stages 1–5 according to eGFR ranges of ≥ 90 , 60–90, 30–59, 15–29, and < 15 mL/min/1.73 m², respectively.

Table 1

Characteristics of patients with and without major cardiac events.

	Cardiac event (+) N = 62		Cardiac event (–) N = 2181		p-Value
Male sex	47	75.8%	1368	62.7%	0.0487
Age, years	69 ± 10		68 ± 10		0.6796
Typical chest pain	15	24.2%	159	7.3%	<0.0001
History of MI	25	40.3%	465	21.3%	0.0006
History of revascularization	26	41.9%	666	30.5%	0.0616
Hypertension	44	71.0%	1486	68.1%	0.7382
Diabetes mellitus	28	45.2%	629	28.8%	0.0082
Hyperlipidemia	18	29.0%	843	38.7%	0.1605
Smoking	21	33.9%	553	25.4%	0.1714
SSS	13.1 ± 8.8		4.9 ± 8.8		<0.0001
SRS	9.6 ± 7.3		3.0 ± 7.3		<0.0001
SDS	6.1 ± 4.0		1.9 ± 4.0		<0.0001
Rest LVEF	51.1 ± 14.7		63.1 ± 14.7		<0.0001
Rest LVEDV	106.5 ± 40.3		78.2 ± 40.3		<0.0001
Rest LVESV	61.5 ± 33.8		32.9 ± 33.8		<0.0001
Stress LVEF	50.0 ± 15.1		62.7 ± 15.1		<0.0001
Stress LVEDV	123.8 ± 44.0		89.8 ± 44.0		<0.0001
Stress LVESV	72.2 ± 38.3		38.4 ± 38.3		<0.0001
eGFR	47.7 ± 29.7		65.5 ± 27.0		<0.0001

MI, myocardial infarction; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; eGFR, estimated glomerular filtration rate.

Statistical analysis

Continuous variables were calculated as means and standard deviations. Intergroup comparisons of continuous and categorical variables were achieved using an unpaired *t* test and the χ^2 test, respectively. Univariate analyses proceeded using a Cox proportional hazards model. Multivariate analyses proceeded using a stepwise Cox proportional hazards model. A χ^2 for trend test was used for detection of a steady proportion of outcomes to categorized interval-independent variables. All data were analyzed using MedCalc Software Version 10.3.0.0 (Mariakerke, Belgium). A *p*-value of <0.05 was considered statistically significant.

Results

Cardiac event rates and clinical characteristics of patients

Sixty-two major cardiac events (cardiac death, *n* = 30; non-fatal MI, *n* = 13; UAP, *n* = 19) developed in 2243 patients with CKD during the first year of follow-up. Table 1 summarizes the characteristics of the patients with and without major cardiac events. The ratios (%) of male to female patients and of patients who developed typical chest pain were significantly higher (*p* = 0.0487 and *p* < 0.0001, respectively), in the group with, than without major cardiac events. Diabetes mellitus and a history of MI were significantly more prevalent in the group with, than without major cardiac events (*p* = 0.0006 and *p* = 0.0082, respectively). However, the ratios of patients with a history of revascularization, hypertension, hyperlipidemia, or smoking habit were similar between the two groups. Myocardial defect scores (SSS, SRS, and SDS) as well as LVEDV and LVESV among QGS parameters in both rest and stress images were significantly higher in the group with, than without major cardiac events (both *p* < 0.0001). In contrast, LVEF in both rest and stress images and the eGFR were significantly lower in the group with major cardiac events (both *p* < 0.0001).

Relationship between SSS and major cardiac event rates

The patients were classified according to SSS grades of normal (*n* = 1455), mildly (*n* = 281), moderately (*n* = 136), and severely (*n* = 371) abnormal to evaluate rates of major cardiac events and survival. The respective incidences of cardiac death at one year were

0.5%, 1.0%, 1.4%, and 4.4%. The cardiac death rate was significantly higher in the group classified as severely abnormal than in those classified as normal (*p* < 0.0001) and mildly abnormal (*p* = 0.0022). The respective incidences of major cardiac events at one year were 1.0%, 3.9%, 5.9%, and 7.3% for normal, mildly, moderately, and severely abnormal groups, respectively. The major cardiac event rates increased in proportion to SSS severity and was significantly higher in the mildly (*p* = 0.0011), moderately (*p* < 0.0001), and severely (*p* < 0.0001) abnormal groups than in the normal group. Typical stress/rest SPECT myocardial perfusion images in patients with cardiac death and without any major cardiac events are shown in Fig. 1.

Prediction of cardiac events

Table 2 shows the results of univariate Cox proportional hazards regression analysis with major cardiac event rates as the dependent variable. Significant variables associated with increased major cardiac event rates were age, male sex, typical chest pain, history of MI, history of revascularization, hypertension, diabetes mellitus, hyperlipidemia, summed defect scores (SSS, SRS, SDS), LVEF, LVEDV, and LVESV in the rest and stress images, and eGFR.

The multivariate Cox proportional hazards regression model analysis indicated diabetes mellitus (*p* = 0.0368), eGFR (*p* = 0.0001), SSS (*p* < 0.0001), and SDS (*p* = 0.0009) as significant independent variables (Table 3).

Association between CKD and major cardiac event rates

Fig. 2 shows the major cardiac event rates during one year among the patients with CKD. The rates of major cardiac event at one year increased in proportion to the progression of CKD stage. The major cardiac event rates were significantly higher in patients with CKD stages 4 (*n* = 67) or 5 (*n* = 102) than in those with CKD stages 1 (*n* = 317; *p* < 0.01) or 2 (*n* = 983; *p* < 0.01). Furthermore, the rates of major cardiac events in the patients with CKD stage 5 were significantly higher than in those with CKD stage 3 (*n* = 774; *p* < 0.01). The patients with CKD stage 5 included 82 (80.4%) who were undergoing hemodialysis.

Fig. 3 shows the major cardiac event rates at one year according to SSS values of <4 and ≥4 among patients with or without diabetes mellitus and/or CKD stages 3 or higher. The major cardiac event

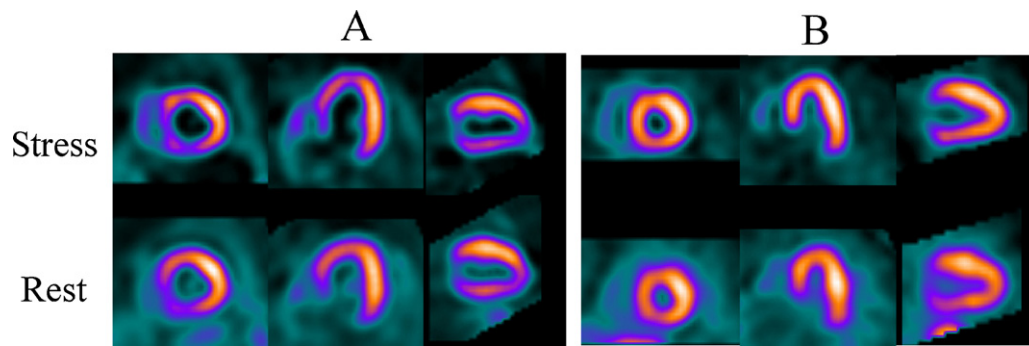


Fig. 1. Typical stress/rest single photon emission computed tomography myocardial perfusion images in patients with cardiac death (A) and without any major cardiac events (B). (A) The image was obtained from a 77-year-old male patient having hypertension, diabetes mellitus, history of myocardial infarction, and estimated glomerular filtration rate (eGFR) = 24.8 mL/min/1.73 m², who died of cardiac events. Hypoperfusion was observed in septal, apex, and inferior segments; the summed stress score (SSS) was 19, the summed rest score (SRS) was 17, and the summed difference score was 2. (B) The image was obtained from a 79-year-old male patient having hypertension and eGFR = 33.8 mL/min/1.73 m², who did not experience any major cardiac events. It indicated normal perfusion with SSS = 0, SRS = 0, and SDS = 0.

Table 2
Univariate Cox proportional hazards regression analysis.

	Chi-square	Hazard ratio	95% confidence interval	p-Value
Age	4.065	1.0194	1.0002–1.0389	0.0438
Male sex	13.261	2.1644	1.3922–3.3650	0.0003
Typical chest pain	13.593	2.7022	1.6856–4.3319	0.0002
Ischemic ECG	1.324	1.3244	0.8341–2.1031	0.2499
History of MI	26.969	2.7688	1.9181–3.9969	<0.0001
History of revascularization	14.210	2.0439	1.4201–2.9418	0.0002
Hypertension	3.896	1.5210	0.9904–2.3359	0.0484
Diabetes mellitus	19.005	2.3076	1.5999–3.3282	<0.0001
Hyperlipidemia	4.781	0.6551	0.4460–0.9623	0.0288
Smoking	0.678	1.1843	0.7969–1.7598	0.4104
Family history	0.202	1.2677	0.4692–3.4253	0.6533
SSS	51.917	1.0583	1.0440–1.0727	<0.0001
SRS	21.218	1.0442	1.0277–1.0611	<0.0001
SDS	49.902	1.1179	1.0894–1.1471	<0.0001
Rest LVEF	46.647	0.9635	0.9542–0.9730	<0.0001
Rest LVEDV	28.070	1.0088	1.0061–1.0114	<0.0001
Rest LVESV	32.045	1.0102	1.0074–1.0130	<0.0001
Stress LVEF	57.989	0.9597	0.9502–0.9692	<0.0001
Stress LVEDV	35.672	1.0089	1.0065–1.0113	<0.0001
Stress LVESV	39.879	1.0101	1.0076–1.0127	<0.0001
eGFR	33.821	0.9780	0.9707–0.9852	<0.0001

ECG, electrocardiogram; MI, myocardial infarction; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; eGFR, estimated glomerular filtration rate.

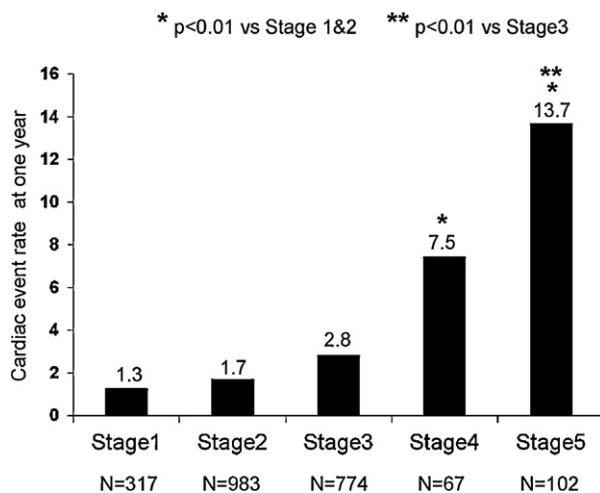


Fig. 2. Incidence of major cardiac events at one year classified according to chronic kidney disease (CKD) stages. Stages 1, 2, 3, 4, and 5 of CKD were taken as estimated glomerular filtration rate ≥ 90 , 60–90, 30–59, 15–29, and <15 mL/min/1.73 m², respectively. Patients with CKD stages 4 or 5 and those with stages 1 or 2 significantly differed. Incidence of major cardiac events was significantly higher in patients with CKD stage 5 than stage 3.

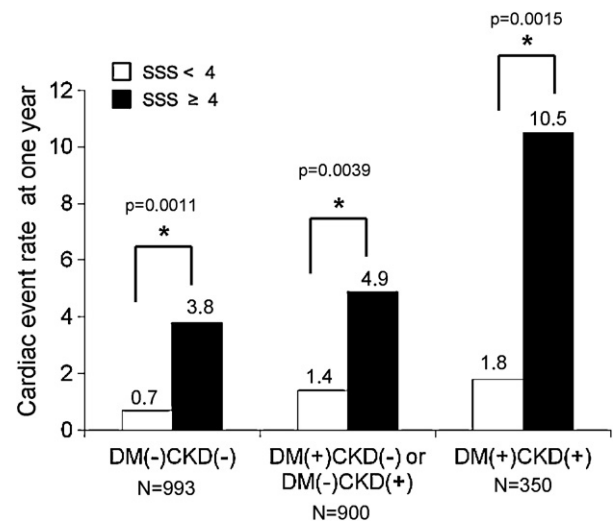


Fig. 3. Incidence of major cardiac events at one year stratified according to summed stress scores (SSS) in patients with or without chronic kidney disease (CKD) and/or diabetes mellitus (DM). Incidence of major cardiac events significantly differed between patients with SSS ≥ 4 and <4 in all combinations.

Table 3

Multivariate Cox proportional hazards regression analysis.

	Hazard ratio	95% confidence interval	p-Value
Diabetes mellitus	1.5080	1.0276–2.2132	0.0368
eGFR	0.9831	0.9755–0.9908	<0.0001
SSS	1.0384	1.0204–1.0567	<0.0001
SDS	1.0548	1.0222–1.0884	0.0009

eGFR, estimated glomerular filtration rate; SSS, summed stress score; SDS, summed difference score.

rates were significantly higher in the subgroups with $SSS \geq 4$ than <4 in all four populations: the patients with both diseases, those with only diabetes mellitus, those with only CKD, and those without both diseases.

Fig. 4 shows the major cardiac event rates at one year according to SSS values of <4 and ≥ 4 among the patients with CKD. There were significant differences in the major cardiac event rates between two sub-groups with $SSS < 4$ and ≥ 4 among the patients with CKD stages 2 and 3. Although the major cardiac event rates were not significantly different between two sub-groups with $SSS < 4$ and ≥ 4 among the patients with CKD stages 1, 4, and 5, the results from chi-square for trend test indicated that the global rates are significantly higher in the sub-group with $SSS \geq 4$ than <4 .

Fig. 5 shows the rates of major cardiac event at one year stratified according to SSS values of <4 and ≥ 4 among patients with eGFR ≥ 60 , 40–59, and <39 . The rates of major cardiac events in the group with eGFR ≥ 60 were 0.8% and 4.9% in the patients with $SSS < 4$ ($n=1056$) and ≥ 4 ($n=246$), respectively. The rates in the group with eGFR 40–59 were 1.7% ($n=481$) and 6.7% ($n=178$), respectively, and 5.0% ($n=199$) and 13.2% ($n=83$), respectively, in the group with eGFR < 39 . The major cardiac event rates increased with decreases in eGFR and the event rates were significantly higher among patients with $SSS \geq 4$ than <4 at every stage of CKD severity.

Discussion

This retrospective large-scale prognostic study assessed the ability of ECG-gated myocardial perfusion SPECT to predict cardiac death, non-fatal MI, and UAP in 2243 Japanese patients with CKD during a one-year follow-up. This study was considerably larger than typical Japanese prospective studies [5,6], and it provided valuable information about the prediction of cardiac event rates in patients with severe CKD including those on hemodialysis. The

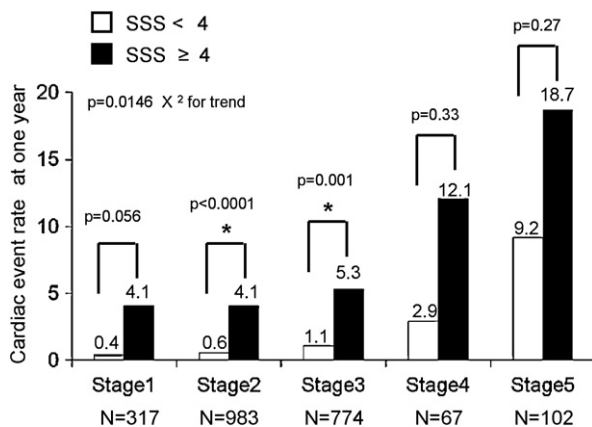


Fig. 4. Incidence of major cardiac events at one year stratified according to summed stress scores (SSS) in patients at each stage of chronic kidney disease (CKD). Stages 1, 2, 3, 4 and 5 of CKD were taken as estimated glomerular filtration rate ≥ 90 , 60–90, 30–59, 15–29, and <15 mL/min/1.73 m², respectively. The major cardiac event rates were significantly different between two sub-groups with $SSS < 4$ and ≥ 4 among the patients with CKD stages 2 and 3.

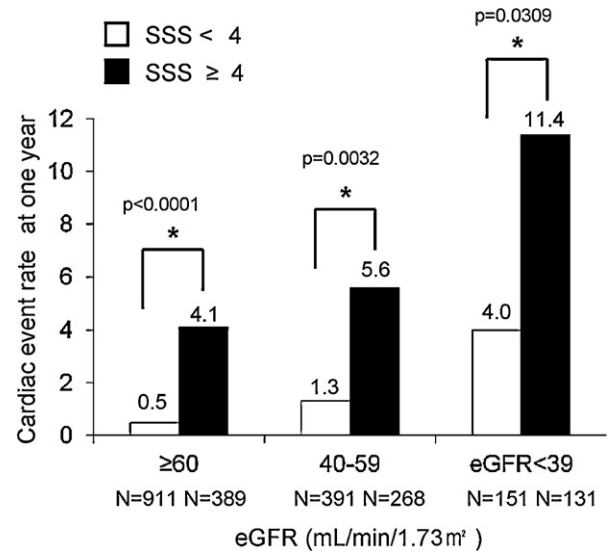


Fig. 5. Incidence of major cardiac events at one year stratified according to summed stress scores (SSS) in patients with renal function based on estimated glomerular filtration rates (eGFR). Incidence of major cardiac events significantly differed between patients with $SSS \geq 4$ and <4 at all levels of renal function.

cardiac event rates at one year increased in proportion to progressive CKD stage and the SSS obtained at a cut-off value of 4 from nuclear cardiology allowed the prediction and risk stratification of cardiac events among patients at all stages of CKD.

European and American scientific articles describe that ECG-gated myocardial perfusion SPECT can predict cardiac events in patients with coronary artery diseases [14–16]. The guidelines produced from a joint collaboration among the American College of Cardiology, the American Heart Association, and the American Society of Nuclear Cardiology, recognize the value of cardiac radionuclide imaging for diagnosis, judging disease severity, risk assessment and prognosis of patients with acute and chronic ischemic syndromes and heart failure, and recommend using ECG-gated myocardial perfusion SPECT for prognostic evaluations of patients with coronary artery diseases [17]. The findings of J-ACCESS by Quantitative Gated SPECT also demonstrated the value of ECG-gated myocardial perfusion SPECT for assessing Japanese patients with suspected or confirmed ischemic heart disease [4].

Hatta et al. [7] performed a sub-analysis of the J-ACCESS database to identify useful predictors of cardiac events in patients with CKD. Although their results demonstrated an incremental value of ECG-gated myocardial perfusion SPECT for predicting cardiac events in patients with CKD, the database did not include patients with end-stage renal disease requiring hemodialysis. Dahan et al. [18] reported that combined dipyridamole-exercise thallium imaging is useful for detecting coronary stenosis and for predicting cardiac events in patients undergoing hemodialysis. Hase et al. [19] performed gated myocardial perfusion SPECT in patients with end-stage renal disease within one month of starting hemodialysis to predict cardiac events. They found that the one-year cardiac event-free survival rate was significantly lower among patients with, than without perfusion defects (34% vs. 96%). However, the prognostic value of ECG-gated myocardial perfusion SPECT remained unknown for patients at all stages including those undergoing hemodialysis and those at the conservative phase of CKD. The present prognostic study, which was as large as J-ACCESS, demonstrated that ECG-gated myocardial perfusion SPECT has prognostic value for predicting cardiac events in Japanese patients with any stage of CKD severity, including those on hemodialysis.

The present results were consistent with previous findings, indicating that the ischemic indexes obtained from gated myocardial

perfusion SPECT are independent significant predictors of cardiac events. Diabetes mellitus was also associated with a prognostic risk, and combination of diabetes mellitus and CKD increased a risk of major cardiac events. These results were similar to those reported by the J-ACCESS groups [7,20,21]. Multivariate Cox proportional hazards regression analysis indicated that eGFR was also a predictor of cardiac events. This evidence, which is consistent with the results of a J-ACCESS sub-study [7], emphasizes that patients on CKD should be managed from the viewpoint of being at high risk for cardiac events. In addition, the cardiac event rate increased as the CKD stage progressed and was particularly high in patients with stage 3 or higher. These results suggest the importance of early management and risk stratification before the CKD stage worsens. Recognition is growing worldwide that CKD should be managed at the early stages to prevent disease progression, reduce complications of a decreased GFR and risk of cardiovascular events, and improve survival and quality of life [22].

We assessed the prognostic risk stratification of cardiac events using ECG-gated myocardial perfusion SPECT in patients at the conservative phase of CKD. The cardiac event rate was significantly higher in all patients in the group with $\text{SSS} \geq 4$ and with mild ($\text{eGFR} \geq 60$), moderate ($\text{eGFR} 40\text{--}59$), and severe ($\text{eGFR} < 39$) CKD compared with the group who had $\text{SSS} < 4$. These findings indicated that the summed defect scores obtained from nuclear cardiology are useful for predicting cardiac events in patients at all stages of CKD.

The follow-up success rate in the present study was 88%, which is relatively lower than the >90% in other follow-up studies [14,16,23] that used a scripted telephone interview to collect follow-up data. We used a posted questionnaire rather than the telephone, because written consent was required to collect medical data from the patients. Despite the lower follow-up success rate, the results of the present study are consistent with those of previous reports, and also provide evidence that patients with CKD stage 5 have a worse prognosis than patients with CKD stages 4 or less.

In conclusion, myocardial perfusion SPECT can contribute to the prediction of cardiac events and survival in patients at all stages of CKD including those on hemodialysis.

Conflict of interest

All authors declare that they have no conflict of interest.

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References

- [1] Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004;164:659–63.
- [2] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296–305.
- [3] Hakeem A, Bhatti S, Dillie KS, Cook JR, Samad Z, Roth-Cline MD, Chang SM. Predictive value of myocardial perfusion single-photon emission computed tomography and the impact of renal function on cardiac death. *Circulation* 2008;118:2540–9.
- [4] Nishimura T, Nakajima K, Kusuoka H, Yamashina A, Nishimura S. Prognostic study of risk stratification among Japanese patients with ischemic heart disease using gated myocardial perfusion SPECT: J-ACCESS study. *Eur J Nucl Med Mol Imaging* 2008;35:319–28.
- [5] Matsumoto N, Sato Y, Suzuki Y, Kunimasa T, Yoda S, Iida J, Nakano Y, Yoshimura A, Miki T, Kato M, Matsuo S, Saito S, Hirayama A. Prognostic value of myocardial perfusion single-photon emission computed tomography for the prediction of future cardiac events in a Japanese population—a middle-term follow-up study. *Circ J* 2007;71:1580–5.
- [6] Ohtaki Y, Chikamori T, Hida S, Tanaka H, Igarashi Y, Hatano T, Usui Y, Miyagi M, Yamashina A. Clinical characteristics in patients showing ischemic electrocardiographic changes during adenosine triphosphate loading single-photon emission computed tomography. *J Cardiol* 2010;55:370–6.
- [7] Hatta T, Nishimura S, Nishimura T. Prognostic risk stratification of myocardial ischaemia evaluated by gated myocardial perfusion SPECT in patients with chronic kidney disease. *Eur J Nucl Med Mol Imaging* 2009;36:1835–41.
- [8] Tanaka H, Chikamori T, Tanaka N, Hida S, Shindo N, Igarashi Y, Yamashina A. A flow-limiting stenosis is the major determinant of exercise-induced myocardial stunning in patients with coronary artery disease. *J Cardiol* 2010;55:337–44.
- [9] Muramatsu T, Nishimura S, Yamashina A, Nishimura T, for the J-ACCESS investigators. Relation between prognosis and myocardial perfusion imaging from the difference of end-point criterion for exercise stress testing: a sub-analysis of the J-ACCESS study. *J Cardiol* 2010;56:51–8.
- [10] Berman DS, Kiat H, Friedman JD, Wang FP, van Train K, Matzer L, Maddahi J, Germano G. Separate acquisition rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography: a clinical validation study. *J Am Coll Cardiol* 1993;22:1455–64.
- [11] Yoda S, Sato Y, Matsumoto N, Tani S, Takayama T, Nishina H, Uchiyama T, Saito S. Incremental value of regional wall motion analysis immediately after exercise for the detection of single-vessel coronary artery disease: study by separate acquisition, dual-isotope ECG-gated single-photon emission computed tomography. *Circ J* 2005;69:301–5.
- [12] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–92.
- [13] Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, Van Train KF, Berman DS. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995;36:2138–47.
- [14] Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998;97:535–43.
- [15] Iskandrian AS, Chae SC, Heo J, Stanberry CD, Wasserleben V, Cave V. Independent and incremental prognostic value of exercise single-photon emission computed tomography (SPECT) thallium imaging in coronary artery disease. *J Am Coll Cardiol* 1993;22:665–70.
- [16] Hachamovitch R, Berman DS, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. *Circulation* 1996;93:905–14.
- [17] Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell Jr RO, Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (ACC/AHA/ASNC Committee to revise the 1995 guidelines for the clinical use of cardiac radionuclide imaging). *Circulation* 2003;108:1404–18.
- [18] Dahan M, Viron BM, Faraggi M, Himbert DL, Legallier BJJ, Kolta AM, Pessione F, Le Guludec D, Gourgon R, Mignon FE. Diagnostic accuracy and prognostic value of combined dipyridamole-exercise thallium imaging in hemodialysis patients. *Kidney Int* 1998;54:255–62.
- [19] Hase H, Joki N, Ishikawa H, Fukuda H, Imamura Y, Saijyo T. Prognostic value of stress myocardial perfusion imaging using adenosine triphosphate at the beginning of hemodialysis treatment in patients with end-stage renal disease. *Nephrol Dial Transplant* 2004;19:1161–7.
- [20] Nakajima K, Matsuo S, Okuyama C, Hatta T, Tsukamoto K, Nishimura S, Yamashina A, Kusuoka H, Nishimura T. Cardiac event risk in Japanese subjects estimated using gated myocardial perfusion imaging, in conjunction with diabetes mellitus and chronic kidney disease. *Circ J* 2012;76:168–75.
- [21] Okuyama C, Nakajima K, Hatta T, Nishimura S, Kusuoka H, Yamashina A, Nishimura T. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for patients with diabetes and chronic kidney disease. *Nucl Med Commun* 2011;32:913–9.
- [22] Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012;379:165–80.
- [23] Abbott BG, Afshar M, Berger AK, Wackers FJT. Prognostic significance of ischemic electrocardiographic changes during adenosine infusion in patients with normal myocardial perfusion imaging. *J Nucl Cardiol* 2003;10:9–16.